Guidance for Industry
Complicated Urinary Tract Infections: Developing Drugs for Treatment

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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> This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of complicated urinary tract infections (cUTIs).[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for treatment of cUTIs. This draft guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective Products, pharmaceutical sponsors, the academic community, and the public.[3]

We consider treatment of cUTI to be an indication distinct from treatment of uncomplicated UTI. This guidance addresses cUTI only. Sponsors interested in pursuing an indication for the treatment of uncomplicated UTI should discuss clinical development plans with the FDA.

This draft guidance revises the draft guidance for industry *Complicated Urinary Tract Infections and Pyelonephritis — Developing Antimicrobial Drugs for Treatment* published in 1998. Once final, this guidance will be considered the FDA's current thinking regarding the development of drugs for the treatment of cUTIs.[4]

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[1] This guidance has been prepared by the Division of Anti-Infective Products and the Office of Biostatistics in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during drug development.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Complicated UTIs (infections involving one or more areas that comprise the urinary tract) are frequently associated with functional or anatomic abnormalities of the urinary tract in men and women and are accompanied by systemic signs and symptoms. Pyelonephritis (infection of one or both kidneys) can occur in persons without functional or anatomic abnormalities of the urinary tract and is considered by the FDA to be a subset of cUTI. The types of bacterial pathogens generally responsible for cUTIs include the Enterobacteriaceae as well as other Gram-negative bacteria and Gram-positive bacteria, including enterococci. Enterobacteriaceae are also the most common bacterial pathogens identified in uncomplicated UTIs. Uncomplicated UTIs are commonly encountered in clinical practice and can occur in otherwise healthy persons, but are not included in the scope of this guidance.

Issues in the design of clinical trials for infectious diseases include the following:

- Clarity in the definition of cUTI

- Adequacy of proposed primary efficacy assessments and time point of the primary efficacy outcome assessments

- Noninferiority versus superiority clinical trial designs

- Choosing and supporting an appropriate noninferiority margin

- Use of prior antibacterial drug therapy

- Use of concurrent antibacterial drug therapy

With these issues in mind, important changes from the draft guidance for industry *Complicated Urinary Tract Infections and Pyelonephritis — Developing Antimicrobial Drugs for Treatment* published in 1998 have been incorporated into the appropriate sections in this draft guidance.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Definition of Complicated UTI

Complicated UTIs are defined as a clinical syndrome characterized by pyuria and a documented microbial pathogen on culture of urine or blood, accompanied by local and systemic signs and symptoms including fever (i.e., oral or tympanic temperature greater than 38 degrees Celsius), chills, malaise, flank pain, back pain, and/or costo-vertebral angle pain or tenderness that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. We consider patients with pyelonephritis, regardless of underlying abnormalities of the urinary tract, to be a subset of patients with cUTIs. Usually, one or more of the following conditions that increase the risk of developing a cUTI are present:

- Presence of a urinary catheter
- 100 mL or more of residual urine after voiding (neurogenic bladder)
- Obstructive uropathy (nephrolithiasis, fibrosis)
- Azotemia caused by intrinsic renal disease
- Urinary retention, including retention caused by benign prostatic hypertrophy

2. Drug Development Population

The intended clinical trial population should be patients with cUTIs. Pyelonephritis is an important distinct subset of cUTI, and approximately 30 percent of the clinical trial population should be patients with pyelonephritis for an indication for "treatment of complicated urinary tract infections including pyelonephritis." A clinical trial population with cUTI, but without an adequate number of patients with pyelonephritis, would support an indication for "treatment of complicated urinary tract infections" (see section III.C.2., Labeling Considerations). Sponsors should discuss pediatric development with the FDA early in clinical development (see section III.B.4.a., Pediatric).

3. Efficacy Considerations

We recommend a primary efficacy endpoint in which response at a fixed time point is defined as both:

- Resolution of clinical symptoms of cUTI

  and

- Microbiological success

We define *microbiological success* as the demonstration that the bacterial pathogen found at trial entry is reduced to less than 10^4 colony forming units per milliliter (CFU/mL) on urine culture. Urine cultures should be processed using a calibrated loop to identify a quantitative count of bacteria at a lower limit of 10^3 CFU/mL rather than using a calibrated loop to identify a quantitative count of bacteria at a lower limit of 10^4 CFU/mL. Most of the patients considered as microbiological success should have no growth of the bacterial pathogen found at baseline (i.e., less than 10^3 CFU/mL), but some patients with 10^3 to 10^4 CFU/mL can also be considered a microbiological success. Sponsors should describe in the protocol how patients in certain clinical situations should be handled in the primary efficacy analysis when they have bacteria identified on quantitative urine culture at 10^3 CFU/mL to 10^4 CFU/mL.[5]

We evaluated the responder endpoint of both microbiological success and resolution of clinical symptoms of cUTI based on a retrospective review of clinical trials data (see section III.B.7, Efficacy Endpoints, and the Appendix). Some of the clinical trials we reviewed defined success as having symptom resolution or symptom *improvement to the extent that no additional antibacterial drug therapy for cUTI was necessary*, but it was not clear what proportion of patients were in the category of having symptom improvement or what proportion of patients had symptoms that completely resolved. In addition, most clinical trials defined microbiological success as a demonstration that the bacterial pathogen found at trial entry was reduced to less than 10^4 CFU/mL on urine culture. Sponsors may wish to prospectively evaluate the responder endpoint in phase 2 trials to better characterize the endpoint, in particular the evaluation of symptom resolution and the evaluation of the proportion of patients that have no growth of bacterial pathogens using a calibrated loop, to identify a quantitative count of bacteria at a lower limit of 10^3 CFU/mL.

We assume that patients with cUTI will have therapy initiated with an intravenous (IV) drug. In general, the safety and efficacy of an investigational drug should be evaluated by maintaining treatment with the investigational drug for the entire duration of treatment, if feasible, and evaluating effectiveness at that time using a well-documented noninferiority margin. For investigational drugs that have only an oral formulation in development for treatment of cUTI, we recommend discussion of the timing of endpoints and noninferiority margins with the FDA before initiation of phase 3 trials. For drugs that have both IV and oral formulations, protocol-

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[5] The normal urinary tract above the urethra is sterile, but the normal urethra may be colonized with bacteria. Thus, bacteria from urethral colonization may enter the urine stream during collection of a urine specimen for culture. Urethral colonizing bacteria are differentiated from true pathogenic bacteria by quantitative urine cultures. The inoculation of a urine specimen using a calibrated wire loop on appropriate agar media, and incubated for 24 to 48 hours, represents a standard technique for quantitative urine culture.

There are two different sizes of calibrated loops that are commonly used in microbiology laboratories to detect a lower limit of bacterial growth on urine culture: 10^3 CFU/mL or 10^4 CFU/mL. In general, bacteria that are found on urine cultures at a quantitative measure of less than 10^4 CFU/mL may be considered to be colonizing or contaminating bacteria, but this depends on the method of specimen collection and clinical presentation of the patient. For the primary endpoint considerations, most culture results following appropriate antibacterial drug therapy should demonstrate no growth (i.e., less than 10^3 CFU/mL) of the baseline bacterial pathogen found at trial entry. However, there may be growth of bacteria that might represent colonization of the normal urethra, that is, bacteria identified on urine culture at 10^3 CFU/mL to 10^4 CFU/mL. Clinical microbiology laboratories follow algorithms to describe the results of a quantitative urine culture at 10^3 CFU/mL to 10^4 CFU/mL as being a contamination of urethral colonizing bacteria or as a true bacterial pathogen. The algorithm and potential clinical situations should be prespecified in the protocol. Regardless of whether a certain clinical situation is considered a microbiological success or not, bacteria identified on urine culture at 10^3 CFU/mL to 10^4 CFU/mL following therapy should be fully evaluated including in vitro susceptibility testing (see section III.B.2., Clinical Microbiology Considerations).

specified criteria for an IV-to-oral switch should be included in phase 3 trials, provided that pharmacokinetic information supports the appropriate doses of both the IV and oral formulations.

For drugs that have only an IV formulation, the IV investigational drug ideally should be maintained for the entire duration of therapy for cUTI, if feasible. However, we recognize that practice guidelines, patient convenience, and risks associated with an indwelling venous catheter will often make the administration of IV antibacterial drug therapy for the entire duration of cUTI treatment difficult or impractical, and there needs to be consideration of IV-to-oral switch to a different oral drug. For investigational drugs that have only an IV formulation in development, we recommend that before trial initiation, sponsors discuss with the FDA whether a switch to an FDA-approved oral antibacterial drug will be planned in clinical trials. As discussed in the Appendix, efficacy evaluations should occur at the fixed time point corresponding to the end of IV investigational drug therapy (i.e., a fixed time point at approximately 5 days). Efficacy evaluations at the fixed time point after all antibacterial drug therapy has been completed should be an important co-primary endpoint.

The Appendix includes a noninferiority margin justification for drugs with only an IV formulation based on a responder endpoint at the completion of IV therapy corresponding to the switch to an FDA-approved oral drug. Although it is important for patients to receive the total duration of therapy for the treatment of cUTI (e.g., between 10 to 14 days of therapy), it is possible that efficacy evaluations after IV therapy has been completed may reflect the effect of the FDA-approved oral drug and not the IV investigational drug. The following example and Table 2 in the Appendix illustrate that the efficacy of the investigational IV drug can be ascertained in this setting, using both interim and later responses:

> Treatment with IV investigational drug for the initial 5 days with assessment of symptom responses and urine cultures at day 5
>
> *then*
>
> Treatment with an FDA-approved oral drug for an additional 5 to 9 days to complete a total of 10 to 14 days of therapy for cUTI, where the oral drug is labeled for the indication of cUTI and practice guidelines specify the duration of therapy for treatment of cUTI is 10 to 14 days with the FDA-approved oral drug. Symptom responses and urine cultures are assessed for efficacy at the fixed time point approximately 7 days after completion of therapy (see section III.B.7.a., Primary efficacy endpoint, for definitions of the primary efficacy endpoints). The results at approximately 14 days after completion of therapy would also be examined.

Sponsors should discuss with the FDA their overall clinical development plans for cUTI and for other infectious disease indications, and whether other clinical trials might lend support for a single adequate and well-controlled trial in cUTI. For the development of treatments for uncomplicated UTIs, further discussion with the FDA is recommended.

4. *Safety Considerations*

The protocol should specify the methods to be used to obtain safety data during the course of the trial. Both adverse event information and safety laboratory data should be collected during the trial. All patients should be evaluated for safety at the time of each trial visit or assessment, regardless of whether the trial drugs have been discontinued. All adverse events should be followed until resolution, even if time on trial has been completed.

A sufficient number of patients, including geriatric patients, should be studied at the exposure (dose and duration) proposed for use to draw appropriate conclusions regarding drug safety. Safety evaluations and assessments should take into consideration the patient populations that are likely to be treated for cUTIs. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations may be needed based on the nonclinical and clinical profile of the specific drug under study. Longer term assessment of adverse events after discontinuation or completion of the antibacterial drug should be considered depending on the specific drug's potential for long-term or delayed adverse effects. If the same dose and duration of therapy for treatment of cUTI was used in clinical trials for other infectious disease indications, the safety information from clinical trials in other infectious disease indications can be part of the overall preapproval safety database. The overall preapproval safety database should contain approximately 700 to 1,500 patients at the dose and duration of therapy for treatment of cUTI, but safety data from trials in other infections that use pertinent doses and durations of treatment could be included.[6]

5. *Pharmacokinetic/Pharmacodynamic Considerations*

The pharmacokinetic/pharmacodynamic (PK/PD) characteristics of the drug should be evaluated using in vitro models or animal models of infection, if not previously performed. Achieving adequate urine drug concentrations to evaluate antibacterial activity in the urine is an important consideration in patients with cUTI. Serum concentration of the drug is also an important consideration because patients with cUTI can have bacteremia and renal parenchymal involvement. The PK/PD characteristics of the drug can be used to guide selection of the dose and dosing interval based on serum and urine concentrations in relation to the minimum inhibitory concentration. Because concentrations can be influenced by renal impairment, sponsors should evaluate the effect of renal impairment on serum and urine concentrations early in clinical development. We recommend that urine drug levels be evaluated in phase 1 and phase 2.

The PK/PD characteristics of the drug (including the relationships to the minimum inhibitory concentrations noted above) should be integrated with the findings from phase 1 PK clinical trials to help identify appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical

[6] A rate of serious and unexpected adverse events that occur at less than 1 in 300 may be a reasonable expectation for a premarketing safety database for a new drug for treatment of cUTI. See the guidance for industry *Premarketing Risk Assessment* for further discussion on sizes of premarketing safety databases. For example, when there are no serious and unexpected adverse events in 1,150 patients, using the Clopper-Pearson method of the estimate of the upper bound of the two-sided 95 percent confidence interval of an adverse event rate, a true rate of serious and unexpected adverse events is likely to be less than 1 in 300 (CJ Clopper and E Pearson, 1934, The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial, Biometrika, 26:404-413).

trials. A dose-response trial design can be considered as an option for clinical trials early in development to weigh the benefits and risks when selecting doses and to ensure that suboptimal doses or excessive doses (beyond those that add to efficacy) are not used in a phase 3 trial, offering some protection against unexpected and unrecognized dose-related toxicity.

Collection of PK data in phase 2 clinical trials can be used to explore the exposure-response relationship and to confirm that the proper dosing regimen is selected for further evaluation in phase 3 clinical trials. Collection of PK data in phase 3 clinical trials may help to explain potential questions regarding efficacy or safety that might arise from the clinical trials. Sponsors should consider a sparse sampling strategy from all patients in clinical trials with cUTIs to allow for the estimation of drug exposure in each patient.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Designs, Populations, and Enrollment Criteria

Patients with cUTIs for whom there is an effective available therapy cannot ethically be enrolled in placebo-controlled trials where some patients receive no antibacterial therapy, even if the placebo period is of a short duration.[7] The clinical trials therefore will be comparative trials designed to show noninferiority or superiority to the active control. The primary analysis will be carried out in patients with organisms sensitive to the investigational drug. The presence of such organisms will not be known at randomization so that the primary analysis will be in a subset of the randomized patients (see section III.B.10.a., Analysis populations). Trial populations should be enriched for patients who are likely to have a bacterial pathogen identified on culture of urine or blood. We recommend the following inclusion and exclusion criteria:

- **Recommended inclusion criteria:**

  - Patients with cUTI with one of the following conditions associated with a risk for developing cUTI:

    - Indwelling urinary catheter
    - Urinary retention (at least 100 mL of residual urine after voiding)
    - Neurogenic bladder
    - Obstructive uropathy
    - Azotemia

    or

  - Patients with pyelonephritis and normal urinary tract anatomy

  and

[7] See ICH E10. This would not prevent a placebo-controlled trial of add-on therapy. In such a trial, all patients would receive antibacterial drug therapy that is considered standard of care. Patients would then be randomized to receive, in addition, an investigational drug or placebo in a trial designed to show added benefit (superiority) of the investigational drug (see section III.B.8., Clinical Trials in Patients With Unmet Need).

- At least two of the following signs or symptoms:

    - Chills or rigors or *warmth* associated with fever (e.g., oral temperature greater than 38 degrees Celsius)

    - Flank pain (pyelonephritis) or pelvic pain (cUTI)

    - Nausea or vomiting

    - Dysuria, urinary frequency, or urinary urgency

    - Costo-vertebral angle tenderness on physical examination

and

- Urine specimen with evidence of pyuria:

    - Dipstick analysis positive for leukocyte esterase

      or

    - At least 10 white blood cells per cubic millimeter

- **Recommended exclusion criteria:**

    - Any recent use (e.g., within 48 hours of enrollment) of an antimicrobial therapy with a drug that has activity in the treatment of urinary tract infection

    - Concurrent use of nonstudy antibacterial drug therapy that would have a potential effect on outcome evaluations in patients with cUTI

    - Patients with suspected or confirmed prostatitis

    - Patients with renal transplantation

    - Patients with ileal loops

    - Patients who are likely to receive ongoing antibacterial drug prophylaxis after treatment of cUTI (e.g., patients with vesico-ureteral reflux)

    - Any recent history of trauma to the pelvis or urinary tract

– Patients with indwelling urinary catheters expected to remain in place after therapy has been completed[8]

– Patients with uncomplicated UTI (generally female patients with urinary frequency, urgency, or pain or discomfort without systemic symptoms or signs of infection)

2. Clinical Microbiology Considerations

Before receipt of clinical trial drug therapy, all patients should submit a urine specimen for culture and in vitro susceptibility testing.

- **Clean-catch mid-stream urine specimen:** After appropriate patient preparation, a specimen should be collected and immediately sent to the microbiology laboratory or properly stored for no longer than 24 hours.[9]

- **Urine specimen from patients with indwelling urinary catheters:** Because biofilms on indwelling catheters (e.g., Foley catheters) are more likely to be present after the catheter has been in place for a period of time, samples should be collected following the placement of a new catheter. If the placement of a new catheter is contraindicated or is not feasible, specimens should be collected using aseptic techniques with the urine obtained through a properly disinfected collection port. Urine samples should never be obtained from the collection bag.

- **Urine evaluations:** A microscopic evaluation (e.g., Gram stain) or dipstick analysis for leukocytes, nitrates, or a catalase test should be performed and the specimen cultured. Sponsors should describe the methods for specimen screening and final reporting of the culture results. In general, bacteria identified at 1 x 10^5 CFU/mL or greater should be considered a bacterial pathogen (probability of true pathogen is greater than probability of contamination). Quantitative urine culture by appropriate methods should be performed using a calibrated loop that would indentify bacteria at a lower limit of 10^3 CFU/mL. In vitro antimicrobial susceptibility testing of the isolates to the investigational drug and to other antimicrobial drugs that may be used to treat UTIs should be performed using standardized methods unless otherwise justified.[10]

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[8] The presence of a chronic indwelling urinary catheter after therapy has been completed may make efficacy endpoints difficult to interpret. For example, some symptoms may not improve or resolve and bacterial pathogens may be present on urine culture after therapy has been completed. If sponsors are considering enrollment of patients with chronic indwelling urinary catheters that are expected to remain in place after therapy has been completed, they should discuss the issues about interpretation of efficacy endpoints in this patient population with the FDA before trial initiation.

[9] See for example American Society for Microbiology, 2007, Manual of Clinical Microbiology, 9th edition or a more recent edition.

[10] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute, Wayne, PA.

- **Other microbiologic considerations:** Aerobic and anaerobic blood cultures should be taken at two separate sterile venipuncture sites before initiation of clinical trial drug therapy.

All isolated bacteria considered to be possible pathogens should be saved in the event that additional testing of an isolate is needed (e.g., pulse-field gel electrophoresis for strain identification). Sponsors conducting trials outside the United States should characterize the pathogen and describe similarities and differences among isolates identified in the United States.

The use of rapid diagnostic tests to determine the presence of bacterial pathogens should be discussed with the FDA before initiation of clinical trials. This may provide a means to enrich clinical trials by enrolling patients with a bacterial etiology or a cUTI caused by a specific type of bacteria. The clinical trials of a new antibacterial drug for treatment of cUTI may provide an opportunity to contribute to the evaluation of a new diagnostic test. Sponsors interested in the development of a rapid diagnostic test should contact the Center for Devices and Radiological Health.

3. Randomization, Stratification, and Blinding

Patients should be randomized at enrollment to the treatments studied in the trial. All trials should be multicenter, well-controlled, and double-blinded unless there is a compelling reason for single-blind or open-label trials. If trials are single-blind or open-label, sponsors should discuss potential biases with the FDA and how these biases will be addressed.

4. Special Populations

a. Pediatric

Sponsors are encouraged to discuss pediatric drug development with the FDA early in the course of clinical development, including the potential for extrapolation of adult efficacy data, appropriate PK studies in pediatric patients to support the selection of a dose, the preapproval safety database in children, and, as appropriate when children are included in clinical trials, the definitions of cUTI in the pediatric population. In general, pediatric patients can be enrolled in cUTIs trials if sufficient safety and preliminary antimicrobial activity data in adults with cUTIs are available and age-appropriate dosing has been well-characterized. If a patient-reported outcome (PRO) instrument is used in the trial, measurement of symptoms in children requires additional PRO instrument development considerations.[11]

b. Pregnant and nonpregnant women

In general, safe and effective treatments are available for pregnant patients with cUTIs. Thus, it is generally appropriate to complete phase 3 clinical trials to establish safety and efficacy in nonpregnant patients, before trials in pregnant patients are initiated. However, if treatment options are not available for pregnant patients with cUTIs (e.g., pregnant patients with bacterial

[11] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

pathogens resistant to all available antibacterial drugs), it may be appropriate to characterize safety and pharmacokinetics in pregnant patients with cUTIs who have the potential to benefit from the investigational drug. Before sponsors consider clinical evaluations of an investigational drug in pregnant women, nonclinical toxicology studies, reproductive toxicology studies, and phase 1 and phase 2 clinical trials should be completed. Infants born to mothers who received the investigational drug should be followed by the trial's investigators until at least 12 months of age.

c. Geriatric

Drug development programs should include a sufficient number of geriatric patients, including patients older than 75, to characterize safety and efficacy in this population.[12]

d. Patients with unmet need

Patients with cUTI and unmet need (e.g., patients who have or are suspected of having a bacterial pathogen with in vitro susceptibility testing that shows resistance to most antibacterial drugs) can be included in drug development programs. See section III.B.8., Clinical Trials in Patients With Unmet Need, for a detailed discussion of clinical trial designs in this population.

5. Dose Selection and Formulations

The findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics, pharmacodynamics, in vitro susceptibility profiles of targeted pathogens, safety information from phase 1 studies, and safety and antimicrobial activity information from phase 2 dose-ranging trials should be integrated for purposes of selecting an appropriate dose or doses to be evaluated in phase 3 clinical trials. An assessment of the drug penetration into the site of action in the urinary tract can be used as supportive evidence that the selected dose is likely to achieve drug concentrations sufficient to exert an antimicrobial and clinical effect (see section III.A.5., Pharmacokinetic/Pharmacodynamic Considerations). In addition, pharmacokinetics of the drug in specific populations (e.g., geriatric patients, patients with hepatic impairment) should be evaluated before initiation of phase 3 trials to determine whether dose adjustments are necessary. This evaluation may help avoid the exclusion of such patients from phase 3 clinical trials.

For drugs that have both an IV and oral formulation, a switch from IV to oral drug during the trial may be appropriate, provided that the pharmacokinetics of the IV and oral formulations have been adequately evaluated to determine appropriate dosing regimens.

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[12] See the ICH guidance for industry *E7 Studies in Support of Special Populations: Geriatrics* and the draft ICH guidance for industry *E7 Studies in Support of Special Populations: Geriatrics; Questions & Answers*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

6. Choice of Comparators

Active-controlled clinical trials for the evaluation of treatment of cUTIs should include an FDA-approved drug for treatment of cUTIs and/or treatment of pyelonephritis. The dosages, regimens, and infusion rates in the labeling should be used.

7. Efficacy Endpoints

a. Primary efficacy endpoint

The primary efficacy endpoint should be a responder outcome:

- **Clinical and microbiologic response:** Resolution of the symptoms of cUTI present at trial entry (and no new symptoms) and microbiological success.[13]

- **Clinical or microbiologic failure:** Symptoms of cUTI present at trial entry have not completely resolved or new symptoms have developed, or the patient has died, or the urine culture taken at any time during or after completion of therapy grows greater than or equal to 10^4 CFU/mL of the original pathogen identified at trial entry.

In general, the fixed time point to evaluate efficacy should be approximately 7 days after completion of antimicrobial therapy for trials using the same duration of antibacterial drug therapy in both treatment groups.[14] As discussed in the Appendix, the timing of this endpoint

[13] Microbiological success is an important component of the responder endpoint because the ascending route of infection is the most common pathophysiological mechanism for cUTI. Continued bacteriuria at greater than 10^4 CFU/mL in patients recently completing treatment for cUTI represents a known risk for enhanced rate of relapse of cUTIs. Hence, microbiological success on urine culture approximately 7 days following completion of therapy, along with resolution of symptoms, is the evidence needed to support a conclusion of treatment benefit (i.e., how a patient feels, functions, and survives). (See, for example, JD Sobel and D Kaye, 2010, Urinary Tract Infections, in GL Mandel, JE Bennett, R Dolin, eds., Principles and Practice of Infectious Diseases, 7th edition, Philadelphia, PA, Churchill Livingstone Elsevier, 957-985.) Although the definition of microbiological success is the reduction of the bacterial pathogen to less than 10^4 CFU/mL on urine culture, most patients should demonstrate no growth at the lower limit of quantitative cultures at less than 10^3 CFU/mL. See section III.A.3., Efficacy Considerations, for a discussion about and a definition of microbiological success. The purpose of conducting quantitative urine cultures so that 10^3 CFU/mL to 10^4 CFU/mL bacteria can be identified includes the potential for additional evaluations such as in vitro susceptibility testing, even among patients that might be considered a microbiological success because the culture result would be interpreted as urethral colonizing bacteria. It would be important to document in vitro susceptibility testing on isolates after completion of treatment even if the isolate represents urethral colonizing bacteria.

[14] The period of observation after completion of antibacterial drug therapy depends on the PK characteristics and half-life of the drug, but in general should be a fixed time point specified in the protocol. In most cases, 1 week after completion of antibacterial drugs should be appropriate for assessment of evidence of efficacy on a primary endpoint and the timing of the endpoint is supported by historical data (see Appendix). Sponsors planning a trial with different durations of therapy between treatment groups should select a fixed time point for the evaluation of the primary endpoint. In addition, we recommend that patients should be evaluated for the responder endpoint during therapy (e.g., day 5 of therapy) even if the responder endpoint during therapy is not a co-primary efficacy endpoint as it is in trials of a switch from an investigational IV drug to an FDA-approved oral drug.

was evaluated for historical evidence of sensitivity to drug effects (HESDE),[15] and a treatment difference to support a noninferiority margin justification was shown for the responder endpoint at the time of assessment of the endpoint. Symptom resolution should include all the core symptoms of cUTI. Baseline symptoms associated with anatomic abnormalities that predispose to cUTI (e.g., symptoms associated with the presence of an indwelling urinary catheter) do not need to be resolved for a consideration of successful responder.

Although clinical trials of an investigational IV drug ideally would evaluate its safety and efficacy for the entire duration of treatment, we were able to find evidence that a treatment effect at a time point of approximately 5 days following IV therapy (see Appendix) for cases where a different oral therapy is used would support efficacy of the IV treatment. If an IV-to-oral switch is incorporated in phase 3 trials for an investigational IV drug, the IV investigational drug should be maintained for a minimum duration (i.e., 5 days of IV therapy) before a switch to oral therapy takes place.

Responder outcome for IV drug therapy when evaluated at day 5 should be as follows:

- **Clinical and microbiological response:** Resolution of the symptoms of cUTI present at trial entry (and no new symptoms) and microbiological success[16] at day 5

- **Clinical or microbiological failure:** Symptoms of cUTI present at trial entry have not completely resolved[17] or new symptoms have developed, or the patient has died, or the urine culture grows greater than or equal to 10^4 CFU/mL at day 5

Any endpoint that includes symptom assessment should use a structured assessment, either a PRO or an interviewer-administered assessment, using an established script for the interview where the interviewer records only those responses given by the patient. If a PRO measure is used, its content validity and other measurement properties should be demonstrated in the population represented in the clinical trial.[18]

A co-primary endpoint for trials incorporating an investigational IV drug with a switch to FDA-approved oral drug therapy should be the maintenance of resolution of the core symptoms of cUTI and microbiological success at a fixed time point approximately 7 days after completion of antimicrobial therapy (see the beginning of this subsection). Because 10 to 14 days of

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[15] See ICH E10.

[16] See section III.A.3., Efficacy Considerations, for a discussion about and a definition of microbiological success.

[17] Sponsors should evaluate symptom improvement and resolution in the context of an endpoint at day 5. For example, all symptoms may be completely resolved except flank pain at day 5 in patients with pyelonephritis, but improvement in flank pain should be substantial such that a switch to oral antibacterial therapy is appropriate and the patient may be considered a clinical responder at day 5. All symptoms should be completely resolved (and urine culture demonstrates that the bacterial pathogen found at entry is reduced to less than 10^4 CFU/mL) at the fixed time point after completion of therapy to be considered a clinical (and microbiological) responder.

[18] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

antibacterial drug therapy is recommended for cUTI,[19] and therapy as short as 5 to 7 days with the use of a fluoroquinolone antibacterial drug is recommended for treatment of pyelonephritis in women without underlying anatomic abnormalities of the urinary tract,[20] clinical trials incorporating a maximum duration of approximately 3 to 4 days of oral drug therapy for pyelonephritis in women without underlying anatomic abnormalities or a maximum duration of oral drug therapy for 5 to 9 days for cUTI allow stronger conclusions about the efficacy of the investigational IV drug therapy given during the initial portion of treatment and also provide therapy consistent with standard of care.

For example, 5 days of IV investigational drug plus 5 days of FDA-approved oral drug for treatment of cUTI provides an appropriate duration of therapy that allows for assessment of the efficacy of the IV investigational drug (when FDA-approved labeling recommends the duration of the oral drug therapy at 10 days for treatment of cUTI). Protocols should indicate the total duration of treatment for patients with cUTI and for patients with pyelonephritis without underlying anatomic abnormalities of the urinary tract because the recommended durations of therapy may be different for certain antibacterial drugs.

Patients achieving complete resolution of the core symptoms of cUTI present at trial entry (and no new symptoms) as reported by the patients themselves should be characterized as a success on a clinical outcome. A PRO instrument (i.e., referring to either a patient-administered or interviewer-administered assessment) using an established script for the interview where the interviewer records only those responses given by the patient could be used to assess aspects of symptom improvement that may be important to patients, including aspects of functioning that are appropriately assessed by the patients themselves. A PRO instrument also may be helpful in evaluating symptom improvement at time points early in the course of therapy, if necessary. If a PRO instrument is used, its content validity and other measurement properties should be demonstrated in the population represented in the clinical trial.[21] Furthermore, issues related to instrument translation and cultural adaptation should be taken into consideration. A well-developed PRO instrument would be optimal for the ascertainment of resolution of symptoms to be used as part of the primary endpoint, but there is at present no such instrument. In the absence of a well-developed PRO instrument, the complete resolution of symptoms as reported by the patient can be used for the clinical response portion of the primary endpoint.

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[19] See the Infectious Diseases Society of America (IDSA) treatment guidelines: Hooton, TM, SF Bradley, DD Cardenas, et al., 2010, Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines From the Infectious Diseases Society of America, Clinical Infectious Diseases, 50:625-663.

[20] See the IDSA treatment guidelines: Gupta, K, TM Hooton, KG Naber et al., 2011, Executive Summary: International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clinical Infectious Diseases, 52:561-564.

[21] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

b. Secondary endpoints

Patients should be evaluated for continued resolution of symptoms and microbiological success at a fixed time point approximately 14 days after completion of antimicrobial therapy. This assessment helps to evaluate sustained microbiological success *and* resolution of all clinical symptoms of cUTI (a responder outcome) as a secondary endpoint. Sponsors should also evaluate the clinical outcome responses and microbiologic outcome responses separately at each fixed time point assessment as secondary endpoints.

8. Clinical Trials in Patients With Unmet Need

Patients with cUTI and unmet need (e.g., patients who have or are suspected of having a bacterial pathogen with in vitro susceptibility testing that shows resistance to most antibacterial drugs) can be eligible for enrollment in a clinical trial designed to show superiority of an investigational drug. The following three conceptual approaches can be considered for superiority clinical trial designs:

1. Patients would be randomized to receive either the investigational drug or a control antibacterial drug treatment that represents standard-of-care therapy. The evaluation of efficacy of the investigational drug would be based on a finding of superiority of the investigational drug on the responder clinical endpoint (described in section III.B.7., Efficacy Endpoints).

2. All patients would receive standard-of-care antibacterial drug treatment chosen empirically or based on the results of in vitro susceptibility testing when available. In addition, patients would be randomized to receive either the investigational drug or matching placebo. The evaluation of efficacy of the investigational drug would be based on a finding of superiority on the responder clinical endpoint in the group that received the investigational drug plus the chosen antibacterial drug treatment versus the group that received placebo plus the chosen antibacterial drug treatment.

3. Patients would be enrolled in a dose-response trial where two doses for which there is equipoise are compared with the goal that one dose group is superior on a responder clinical endpoint.

We encourage sponsors considering superiority clinical trial designs in patients with cUTI and unmet need (e.g., cUTI caused by bacteria resistant to multiple antibacterial drugs) to discuss the protocol design with the FDA during protocol development. A data monitoring committee (DMC) generally should be in place to perform interim effectiveness analyses for success or futility and be prespecified in the protocol and in the analysis plan (see section III.B.10.f., Interim analyses and data monitoring committee).

9. Trial Procedures and Timing of Assessments

a. Entry visit

At the entry visit, the following information should be captured and recorded on the case report form:

- History and physical examination

- Prior and concomitant drugs

- Baseline clinical signs and symptoms of cUTI including vital signs

- Microbiologic specimen: an adequate clean-catch urine specimen for culture (or other appropriate method to collect a urine culture that minimizes risk of bacterial contamination); blood cultures (using aseptic techniques, aerobic and anaerobic blood cultures obtained at two separate venipuncture sites before administration of antibacterial therapy)

- Microscopic evaluation of urine specimen (urinalysis)

- Laboratory tests as appropriate (e.g., complete blood cell count, serum electrolytes, serum liver enzymes, renal ultrasound, or other tests as appropriate)

b. On-therapy visit on trial days 3 to 7

Patients should be evaluated early in the course of treatment to assess for clinical failure, where rescue antibacterial drug therapy is appropriate, or clinical improvement. This visit should also capture clinical observations such as vital signs, physical examination findings, laboratory test results, adverse events, and patient symptoms using a PRO instrument, if such an instrument is qualified or is being evaluated for its potential qualification. An on-therapy visit at the time of IV-to-oral switch should have a urine specimen obtained for microscopic examination and culture as well as clinical observations and patient symptoms. The evaluations at the end of IV therapy should form the basis of the co-primary endpoint in trials evaluating an IV investigational drug with an IV-to-oral switch.

c. End-of-treatment visit

Patients should be evaluated at the end of prescribed therapy. Laboratory assessments for safety should be performed at this visit. If the trial drug needs to be continued beyond the protocol-specified duration, objective criteria for extending therapy should be prespecified in the protocol. Patients without clinical improvement or with progression of signs and symptoms of cUTI should be considered as failures and rescue antibacterial drug therapy should be provided.

d. Post-treatment visit 7 days after completion of therapy

The primary responder endpoint should be evaluated at the post-treatment visit. Patients should be evaluated by history and physical examination for clinical signs, including vital signs, at this visit. Patients should be assessed at this visit for symptom resolution, as one component of the responder primary endpoint. A urine specimen should be obtained for microscopic examination and culture.

e. Late post-treatment visit 14 days after completion of therapy

Patients with cUTIs should be assessed for the maintenance of clinical response at the late post-treatment visit.

f. Rescue antibacterial drug therapy

Any patient with a cUTI characterized as clinical and/or microbiologic failure during treatment with the clinical trial drugs should receive appropriate antibacterial drug therapy. The results of all microbiology cultures and drug susceptibility testing (see section III.B.2., Clinical Microbiology Considerations) should be provided to the treating clinicians to assist in the choice of rescue antibacterial drug therapy for the patient. Patients who receive rescue antibacterial drug therapy should continue to have protocol-specified trial visits.

10. Statistical Considerations

The trial's primary and secondary hypotheses and the analysis methods should be prespecified in the protocol and in the statistical analysis plan, and should be finalized before trial initiation.

a. Analysis populations

The following definitions apply to various analysis populations in cUTI clinical trials:

- **Intent-to-treat (ITT) population:** All patients who were randomized.

- **The microbiological intent-to-treat population (micro-ITT population):** All randomized patients who have a baseline bacterial pathogen on culture of urine or blood that causes UTI against which the investigational drug has antibacterial activity. Patients should not be excluded from this population based upon events that occurred post-randomization (e.g., loss to follow-up).

- **Clinically evaluable or per-protocol populations:** Patients who meet the definition for the ITT population and who follow important components of the trial as specified in the protocol.

- **Microbiologically evaluable populations:** Patients who meet the definition for the micro-ITT population and who follow important components of the trial as specified in the protocol.

- **Safety population:** All patients who received at least one dose of drug during the trial.

The micro-ITT population should be considered the primary analysis population. Consistency of the results should be evaluated in all populations and any inconsistencies in the results of these analyses should be explored and explanations provided in the final report.

b. Noninferiority margins

A noninferiority clinical trial design with a prespecified noninferiority is the most likely design that would be used in the evaluation of an investigational antibacterial drug for cUTI. The noninferiority margin can be supported based on HESDE of the control antibacterial therapy considering the responder endpoint of microbiological success and resolution of clinical symptoms in trials of patients with cUTI at a fixed time point approximately 7 days after completion of antimicrobial therapy. For the evaluation of an IV investigational drug, the noninferiority margin to be supported would be microbiological success and resolution of clinical symptoms early in the course of therapy at the time of the switch from IV to oral therapy (i.e., at approximately 5 days of IV therapy). The Appendix describes an overview of the basis for selecting a noninferiority margin for cUTI. It will be apparent that the effect of antibacterial drugs is fairly large compared to no treatment, so that M_1, the margin that would assume some degree of effectiveness compared to placebo, is also relatively large, probably at least 30 percent. Loss of that much of the effect of the control, however, would not be clinically acceptable (see paragraph below), so that the clinically acceptable margin, M_2, will be smaller.

For a noninferiority trial, the primary endpoint analysis should be the comparison between treatment groups of the proportion of clinical and microbiologic responders at approximately 7 days after completion of therapy, or at the time of the switch from IV to oral drug therapy at approximately 5 days for trials evaluating an IV investigational drug. Sponsors should support the noninferiority margin for the proposed trial design and patients enrolled, considering the limitations and uncertainties of the rates of clinical resolution and microbiological success used to determine the HESDE. In most cases, a noninferiority margin of 10 percent will be clinically acceptable and scientifically justified. Sponsors should submit the justification for their choice of the noninferiority margin with phase 3 protocols. When the trial is completed, the applicability of the HESDE to the actual patient population enrolled in the trial should be assessed in the final clinical trial report. It should be appreciated that showing superiority in a trial designed as a noninferiority trial requires no statistical correction, but that reaching a conclusion of noninferiority in a superiority trial generally is difficult. Therefore, it is generally appropriate to design a noninferiority trial.[22]

[22] For more information about the design and approaches to the noninferiority clinical trial, see the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

c. Sample size

The appropriate sample size for a clinical trial should be based upon the number of patients needed to answer the prespecified hypothesis posed by the trial. The sample size is influenced by several factors, including the prespecified type I and type II error rates, estimate of the control response rate, the noninferiority margin, or the magnitude by which the investigational drug is expected to be superior (for a superiority trial). The appropriate sample size should be estimated using a two-sided type I error rate of 0.05 ($\alpha=0.05$). An example of the sample size estimation for a noninferiority trial is included in the Appendix.

d. Missing data

There is no optimal way to deal with missing data in clinical trials. Sponsors should make every attempt to limit loss of patients from the trial by incorporating strategies for adequate follow-up and these strategies should be specified in the protocol. Patients who do not complete the trial may differ substantially from patients who remain in the trial in both measured and unmeasured ways, posing analytic problems. The way missing data will be handled should be specified in the protocol. Patients who stop trial drug and initiate rescue therapy generally would be counted as nonresponders or failures, but should be followed. Sponsors should prespecify several sensitivity analyses to assess the robustness of the primary analysis, including analyses with multiple imputation methods and classification of all missing outcomes as failures. However, all of these methods depend on uncertain assumptions, and interpretation of trial results may be difficult if there is a high rate of missing data or the rates of missing data are different across treatment arms.

e. Statistical analysis plan

Before initiation of any phase 3 trial, sponsors should provide a detailed statistical analysis plan with the protocol for the phase 3 trial.

f. Interim analyses and data monitoring committee

If interim effectiveness analyses for success or futility will be performed, they should be prespecified in the protocol and in the analysis plan along with a justification. Details on the operating procedures also should be provided before trial initiation. The purpose of the interim analysis should be stated along with the appropriate statistical adjustment to control the overall type I error rate. It is important that an appropriate firewall be in place to guarantee that the interim analysis will not affect trial conduct and thereby compromise trial results. This can be accomplished by creating an independent DMC that monitors the protocol with prespecified operational procedures. Such a committee also might be created if there were safety concerns about the drug or the treatment approach. If a DMC is used, a detailed charter with the composition of the committee members, conflicts of interest, decision rules, details on the measures taken to protect operational bias and the integrity of the trial, and the standard operating procedures should be provided for review.[23]

[23] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

C. Other Considerations

1. Relevant Nonclinical Considerations

New antibacterial drugs being studied for cUTIs should have nonclinical data documenting activity against commonly implicated pathogens for cUTI.[24] Animal models of cUTIs may contribute to demonstrating proof of concept for the treatment of cUTIs and for evaluating antibacterial activity. Animal studies should not be considered a substitute for clinical trials in patients with cUTIs that must be conducted to evaluate safety and efficacy of the drug (21 CFR 314.600).

2. Labeling Considerations

The labeled indication under the INDICATIONS AND USAGE section should reflect the patient population enrolled in the clinical trials. For consideration of an indication for "treatment of complicated urinary tract infections and pyelonephritis," we recommend that approximately 30 percent of the patient population in the cUTI clinical trials have a diagnosis of pyelonephritis.

[24] See the draft guidance for industry *Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation*. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

APPENDIX: JUSTIFICATION FOR NONINFERIORITY MARGIN FOR COMPLICATED URINARY TRACT INFECTIONS

The first step in determining a noninferiority margin is determining that the control treatment had a consistent effect in past studies (i.e., HESDE). In the present case, the usual source of HESDE, past controlled trials, is not available. Instead, we make use of cure rates in the pre-antibacterial era and compare those with cure rates in antibacterial drug trials. This Appendix describes reports in the literature on the natural history of cUTIs before the availability of antibacterial drugs. In addition, responder outcomes were assessed from completed clinical trials that were conducted within the past 2 decades. We compared the two sources of information to arrive at an estimate of the treatment effect of antibacterial drug therapy on outcomes in patients with cUTI. Sponsors should consider the information presented in this Appendix when considering an active-controlled trial designed for noninferiority.

A literature search was performed using combinations of search terms such as the following: *placebo*, *urinary tract infections*, *drug therapy*, *anti-infective agents*, and *antibacterial agents*. A PubMed search identified 131 articles, and other historical literature databases identified 9 articles. Of the 140 articles, there were no placebo-controlled studies for the treatment of cUTI. The search found only active-controlled studies for cUTI. Of the nine articles identified in the historical database searches, one review paper referenced several additional historical articles. Those articles in turn referenced other historical articles. Overall, 13 articles were identified that contained information about treatment effects before the availability of antibacterial drugs (i.e., before 1930). Four articles are best described as a case series of patients in which the clinical courses of patients with cUTIs were outlined; the other nine articles provided general overviews of different treatments that were available at the time.

A total of seven recently conducted clinical trials were identified that evaluated drugs approved for treatment of cUTI and had sufficient data to assess clinical outcomes and microbiologic outcomes on individual patients after a period of observation following completion of antibacterial drug treatment (end of therapy). Four of the seven clinical trials evaluated IV antibacterial drugs including an oral switch and had sufficient data to assess outcomes on individual patients at the time of the IV-to-oral switch (end of IV therapy). We begin with a description of the natural history of cUTI.

Natural History of cUTI Before the Availability of Antibacterial Drugs

Four articles describe the natural history of cUTI without the use of antibacterial drugs based on uncontrolled observational data.

1. Culver, H, RD Herrold, FM Phifer, 1918, Renal Infections: A Clinical and Bacteriologic Study, Journal of the American Medical Association, 70:1444-1448.

This article summarized 116 consecutive patients hospitalized for treatment of cUTI. Patients with urinary tract infections caused by tuberculosis were excluded. Chills and fever, back pain, and painful urination were the most common symptoms reported. The therapy at that time was targeted to alter the pH of the urinary tract and exert an antibacterial effect (e.g., administration of alkali in the form of sodium citrate). Approximately 90 percent of infections were caused by "the colon bacillus" (i.e., most probably *Escherichia coli*). The authors defined clinical response as follows: "Our standard for judging a complete cure was not merely complete relief of symptoms, but two successive negative cultures from five to seven days apart." Approximately 83 percent of patients completed therapy within a 1-month time frame, based on the discussions of the types of treatments administered to the patients. The remainder received treatment for more than 1 month. However, we considered all patients in this observational cohort to have received a duration of therapy and efficacy assessments that were similar to the duration of antibacterial drug therapy in a trial conducted today (i.e., approximately 2 weeks of antibacterial drug therapy followed by a period of observation of approximately 1 week). The authors stated that 30 patients (25.9 percent) were cured after the course of treatment was completed. Note that cure was defined by the endpoint of microbiological success *plus* resolution of clinical symptoms.

2. Henline, RB, 1925, Hexyl Resorcinol in the Treatment of 50 Cases of Infections of the Urinary Tract, J Urol, 14:119-133.

This article described 38 infections of the urinary tract caused by bacterial pathogens responsible for cUTI (12 patients had gonorrhea and were excluded from the review). Most patients had evidence of obstructive uropathy. Attempts were made to correct the obstructive uropathy (e.g., via urethral dilation) before treatment was started. Hexylresorcinol's mechanism of antibacterial activity is not entirely characterized, but it appears to act, in part, by lowering surface tension in the urinary tract. Treatment was given on average for more than 1 month, with an average of 6 months for patients with infections caused by the "colon bacillus" and an average of 9 months for patients with infections caused by other bacteria.

Cure was defined by the authors as negative cultures of urine obtained during cystoscopy of the bladder (microbiological success). The authors described their results as the number of days until negative urine cultures were obtained via cystoscopy. The resolution of clinical symptoms was not systematically recorded in the paper, but the few clinical vignettes in the paper indicate that patients had resolution of clinical symptoms along with microbiological success. We considered patients as having a successful outcome if microbiological success was obtained within 1 month.

In addition to excluding patients with gonorrhea, we also excluded seven patients who had acute or chronic prostatitis. Out of a total of 31 patients with cUTI, there was microbiological success in 7 patients (22.6 percent) within 30 days of therapy in this case series. When we considered microbiological success at an earlier time point (e.g., after 7 days of therapy), there did not appear to be any patients who had microbiological success at 7 days.

3. Koll, IS, 1911, An Experimental and Clinical Study of the Colon Bacillus Infections of the Urinary Tract, J Urol, VII(11):417-428.

The authors describe a case series of patients with cUTI infections, either "pyelonephritis" or "cystitis." We considered patients with cystitis to have cUTI (and not uncomplicated UTI) because the duration of symptoms in this study was between approximately 4 weeks and several years, with only one person having symptoms lasting for a short period of time (1 week) before presentation for treatment. Treatment was aimed at altering the urinary pH to exert a potential antibacterial effect. For example, treatment consisted of instillation of aluminum acetate into the bladder. The authors reported successful outcomes for all patients in this study. However, treatments were administered for weeks or months before microbiological success was noted. We considered the outcome in the study to be successful if therapy was administered for less than 4 weeks and microbiological success was observed at the end of treatment. Of the 15 patients in this study, 4 (26.7 percent) had microbiological success within 4 weeks of therapy. When we considered microbiological success at an earlier time point (e.g., within 1 week of therapy), there did not appear to be any patients who had microbiological success at 1 week of therapy.

4. Todd, R, 1857, Clinical Lectures on Certain Diseases of the Urinary Organs and on Dropsies, Philadelphia: Blanchard and Lea, 243-261.

This textbook chapter appears to be a transcript of medical lectures at a teaching hospital. These lectures describe clinical outcomes among patients with cUTIs. This book was published at a time before the recognition of bacteria as a cause for disease. All 10 patients were described as having purulent material from the urine and, therefore, represented patients with cUTI. Five patients died while hospitalized. Three patients (30 percent) appeared to have spontaneous recovery of their symptoms within a 4-week time period. It should be noted that these three patients had symptoms that lasted for years before presentation for treatment at this hospital, and the treatment appeared to be drainage of a perinephric abscess (“drained kidney tumor”) or relief of a ureteral obstruction. Thus, these three patients experienced complications from untreated cUTI before presentation for medical care at this hospital.

Table 1 provides a summary of the results of the four articles. For three articles that did not describe a responder endpoint, we chose to consider *microbiological success + clinical response* as representing the greatest proportion that could have achieved both microbiological success and resolution of clinical symptoms. Overall clinical and microbiological success in these pre-antibacterial studies was no higher than 30 percent. As noted in the table, an upper bound for meta-analysis of the results is about 33 percent.

890 **Table 1. Summary of Studies of cUTI Before Antibacterial Drug Therapies**
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Study	Population	Timing of Evaluation	Microbiological Success	Clinical Response	Microbiological Success + Clinical Response	Endpoint Specified in the Paper	Notes
Culver 1918	Adults with cUTI	83% completed the nonantibacterial therapy within approximately 1 month	Not provided	Not provided	30/116 (25.9%)	Complete relief of symptoms and two successive cultures reported as *negative* separated by 5-7 days	1, 2
Henline 1925	Adults with cUTI	Nonantibacterial therapy administered until negative cultures	7/31 (22.6%)	Not provided	Not provided ≤ 7/31 (22.6%)	*Negative* urine cultures obtained by cystoscopy	2
Koll 1911	Adults with cUTI	Nonantibacterial therapy administered until sterile urine obtained	4/15 (26.7%)	Not provided	Not provided ≤ 4/15 (26.7%)	*Sterile* urine cultures	2
Todd 1857	Adults with cUTI	Supportive therapy and what appears to be drainage of perinephric abscess or relief of urerter obstruction	Not provided	3/10 (30%)	Not provided ≤ 3/10 (30.0%)	Not specified, in general relief of symptoms	3
DerSimonian and Laird random effects meta-analysis for the microbiological success + clinical response: 25.6% (95% CI: 19.6%, 32.7%)							4

892 [1] This paper provides the best estimate of an endpoint of both clinical and microbiological cure for patients with cUTI treated without
893 antibacterial drug therapy.
894 [2] Therapies at this time consisted of altering the urinary pH or altering surface tension that may have resulted in an indirect antibacterial effect.
895 Patients had symptoms of cUTI for months or in some cases years before presenting for treatment.
896 [3] Later in the 1800s, the germ theory of disease was described by Louis Pasteur and Robert Koch.
897 [4] DerSimonian, R and N Laird, 1986, Meta-Analysis in Clinical Trials, Control Clin Trials, 7:177-187.
898

Evaluation of Recently Conducted Phase 3 Trials of cUTI for End of Therapy

We evaluated the results of phase 3 trials in patients with cUTI that were submitted to the FDA to support an application for approval for treatment of cUTI, including pyelonephritis. Table 2 includes the active-controlled drugs approved for treatment of cUTI as well as investigational drugs that were approved for treatment of cUTI based on these successful trial results. The trials reported microbiological success and investigator-assessed clinical responses for individual patients at time points ranging between 3 to 10 days after completion of antibacterial drug therapy. In general, antibacterial drug therapy was administered for approximately 2 weeks. Overall, the evaluations were performed within 1 month after the initiation of therapy (e.g., study day 24 following 14 days of antibacterial drug therapy and a 10-day period of observation after completion of therapy). Microbiological success for all of these trials was defined as having less than 10^4 CFU/mL on quantitative urine cultures. Clinical response was defined, in general, as complete resolution of symptoms or improvement in symptoms such that no additional antibacterial drugs were required. Some trials in Table 2 have two treatment groups and each group is displayed separately. The analyses are based on the micro-ITT population (i.e., all patients with a documented bacterial infection).

Table 2. Summary of Phase 3 Trials in Patients With cUTI; Micro-ITT Populations

Study	Day of Evaluation	Microbio-logical Success	Clinical Response	Microbiological Success + Clinical Response	Source
1	7-10 d post-Rx	171/208 (82.2%)	188/208 (90.4%)	164/208 (78.8%)	Trial datasets
2	7-10 d post-Rx	149/192 (77.6%)	166/192 (86.5%)	139/192 (72.4%)	Trial datasets
3	5-9 d post-Rx	197/227 (86.8%)	185/227 (81.5%)	180/227 (79.3%)	Trial datasets
	5-9 d post-Rx	209/248 (84.3%)	206/248 (83.1%)	197/248 (79.4%)	Trial datasets
4	5-9 d post-Rx	106/139 (76.3%)	112/139 (80.6%)	104/139 (74.8%)	Trial datasets
	5-9 d post-Rx	54/73 (74.0%)	55/73 (75.3%)	51/73 (69.9%)	Trial datasets
5	6-9 d post-Rx	257/325 (79.1%)	291/325 (90.0%)	241/325 (74.2%)	Trial datasets
	6-9 d post-Rx	253/323 (78.3%)	260/323 (80.5%)	233/323 (72.1%)	Trial datasets
6	6-9 d post-Rx	278/337 (82.5%)	294/337 (87.2%)	255/337 (75.7%)	Trial datasets
7	3-9 d post-Rx	240/317 (75.7%)	224/317 (70.7%)	201/317 (63.4%)	Trial datasets
	3-9 d post-Rx	229/302 (75.8%)	205/302 (67.9%)	193/302 (63.9%)	Trial datasets
DerSimonian and Laird random effects meta-analysis for the microbiological success + clinical response: 73.2% (95% CI: 69.6%, 76.6%) (See note 4 at the bottom of Table 1.)					

Overall, the rate of microbiologic and clinical success was not lower than 63 percent and the mean response in the meta-analysis was 73 percent with a lower bound of the 95 percent confidence interval at almost 70 percent.

Treatment Effect and Support for Noninferiority Margin for End of Therapy

An estimate of the treatment difference can be derived from comparing the upper bound of the rate of the microbiological success plus clinical resolution noted before antibacterial drug therapies were available (approximately 33 percent from Table 1), and the lower bound of the rate of the microbiological success plus clinical resolution from recently conducted clinical trials of antibacterial drugs (approximately 69 percent from Table 2). There is thus clear evidence of an effect of the active control (i.e., HESDE) and the treatment difference is estimated to be 36 percent (69 percent minus 33 percent).

Based on this type of comparison of outcomes, a treatment effect of approximately 36 percent can be supported for a responder endpoint of microbiological success plus clinical resolution at a fixed time point approximately 7 days after completion of therapy. This is the principal basis for determining M_1, so long as the constancy assumption is reasonable. When determining M_1, there are a number of limitations in the comparison of four articles in the period of time before availability of antibacterial drug therapy to recently conducted clinical trials:

- The natural history of untreated or inadequately treated cUTI was derived using 3 observational studies from nearly a century ago and 1 paper describing patients from approximately 150 years ago.

- There was a lack of clarity for the endpoint of microbiological success plus clinical resolution from the natural history data.

- The definitions for clinical responses in the recently conducted trials included symptom improvement such that no additional antibacterial drug therapy was required. In some trials, symptoms were assessed by the clinical investigator on a case report form. (We now recommend that symptoms be assessed directly by the patient through use of a patient-reported or interviewer-based format.)

- The type and duration of treatments differed greatly among the studies describing the natural history.

- Patients with cUTI from the natural history studies often had months or years of symptoms before presenting for treatment. The patients under evaluation at that time may represent a population different from patients enrolled in clinical trials today.

- Only one of the natural history studies included patients with pyelonephritis; all of the recently conducted trials included patients with pyelonephritis.

We note strengths associated with this analysis of HESDE below:

- The endpoint of microbiological success plus complete clinical symptom resolution was clearly outlined for one of the historical papers.

- For the two historical papers that described only microbiological success, we assumed that all patients who had microbiological success also had clinical resolution. For the historical paper that described only clinical resolution, we assumed that all patients who had clinical resolution also had microbiological success. Based on recently conducted trials, there will be some patients who have microbiological success yet have continued symptoms, as well as patients who have resolution of symptoms yet have continued bacterial pathogens identified on quantitative urine culture. Therefore, the estimate of the proportion of patients achieving both microbiological success and clinical resolution of symptoms from untreated or inadequately treated historical studies of cUTI was the largest estimate that was possible.

- The historical therapies to alter the urinary tract pH or alter surface tension may have had some antibacterial effects, leading to a possible overestimate of the rate of favorable outcomes of the natural history of cUTI, leading to a more conservative estimate of the treatment difference.

- The favorable outcomes from each of the historical studies were similar and were achieved in only 20 to 30 percent of patients, compared to the much greater favorable outcome rates with antibacterial treatment, which indicates that the estimated 35 percent or greater treatment effect at a time point after a period of observation following completion of antibacterial therapy is robust.

- The more recently conducted phase 3 trials had patient-level endpoints from datasets reviewed by FDA medical and statistical reviewers; the point estimates of the proportions of patients with the responder outcome of microbiological success and clinical response from the trials were similar regardless of the type of antibacterial drug used for treatment of cUTI.

Overall there is strong support for HESDE based on a responder outcome of symptom resolution and microbiological success. The responder includes symptom resolution and thus directly captures clinical benefit (i.e., how a patient feels, functions, and survives). An endpoint defined only by microbiological success (a reasonably persuasive surrogate endpoint but not a direct measure of clinical benefit) would not have that property. We chose to recommend a responder endpoint that includes both clinical and microbiological endpoints for the noninferiority trial design because the two components of the responder endpoint are highly relevant and plausible; moreover, as patients with asymptomatic bacteriuria who recently complete treatment for cUTI are at high risk for recurrence or relapse of cUTI, it is important to determine microbiological endpoints.

For the selection of a noninferiority margin, a large proportion of M_1 should be preserved to maintain the important treatment effects of antibacterial drugs in the treatment of cUTI. Thus, a noninferiority margin (M_2) of 10 percent can be supported for active-controlled clinical trials of cUTI using a responder endpoint of microbiological success plus clinical resolution at a fixed time point approximately 7 days after completion of therapy, in the patient population with microbiologically documented cUTI.

Evaluation of Recently Conducted Phase 3 Trials of cUTI for End of IV Therapy

We evaluated patient-level data from phase 3 IV-to-oral-switch trials in patients with cUTI that were submitted to support an application for approval of an IV drug. The trials provided specific clinical and microbiological criteria for switching from IV to oral therapy. In general, patients were required to have microbiological success on therapy and to have achieved improvement in clinical symptoms before switching to oral therapy. We considered clinical response as having complete resolution of symptoms of cUTI at the timing of the IV-to-oral switch (i.e., resolution of dysuria, frequency, suprapubic pain, urgency, and flank pain, which were evaluated in all trials). In addition, some trials also required that patients should not have nausea or vomiting upon switching to oral therapy. The information on resolution of nausea or vomiting was not recorded on case report forms and therefore was not used as a specific symptoms response or resolution in the trials' electronic datasets. Table 3 provides a summary of the trials that incorporated an IV-to-oral switch and evaluated symptom responses at the timing of the IV-to-oral switch.

Table 3. Summary of Phase 3 Trials Evaluating Responses at End of IV Therapy

Study Group	Mean Duration of IV Therapy	Microbiological Success During Treatment With IV	Clinical Response at End of IV Therapy*	Microbiological Success + Clinical Response	Source
1	4.0 days	100%	106/216 (49.1%)	106/216 (49.1%)	Trial datasets
2	4.1 days	100%	113/230 (49.1%)	113/230 (49.1%)	Trial datasets
3	4.0 days	100%	87/130 (66.9%)	87/130 (66.9%)	Trial datasets
4	4.0 days	100%	47/67 (70.1%)	47/67 (70.1%)	Trial datasets
5	5.4 days	100%	230/317 (72.5%)	230/317 (72.5%)	Trial datasets
6	5.3 days	100%	224/311 (72.0%)	224/311 (72.0%)	Trial datasets
7	5.5 days	100%	230/329 (69.9%)	230/329 (69.9%)	Trial datasets
DerSimonian and Laird random effects meta-analysis for the microbiological success + clinical response: 64% (95% CI: 56%, 72%) (See note 4 at the bottom of Table 1.)					

* The five symptoms that were evaluated as having complete resolution in this analysis were symptoms evaluated among all seven study groups: dysuria, frequency, suparpubic pain, urgency, and flank pain.

Treatment Effect and Support for Noninferiority Margin for End of IV Therapy

Two observational studies in Table 1 collected serial urine cultures and reported the time to demonstration of microbiological success on urine culture for individual patients. The earliest time of the report of the first demonstration of microbiological success in an individual patient was 15 days in one study and 2 weeks in the other study. Although the articles did not report the results of each urine culture that was obtained, we can infer that patients receiving nonantibacterial therapies for cUTI would be unlikely to have microbiological success early in therapy (i.e., within 1 week). Recently conducted antibacterial drug trials have shown that all patients have microbiological success during the administration of IV antibacterial drugs (mean duration of IV therapy was 4 or 5 days before the switch to oral drug therapy). The trials also demonstrate that a sizable proportion of patients with cUTI have resolution of symptoms at the earlier time point at the time of IV-to-oral switch.

Acknowledging the limitations previously listed, and making an additional conservative assumption about the historical articles that the microbiological success plus clinical response rates would be similar (certainly not greater) for a much earlier time point (e.g., day 5 when it may be unlikely that any patient would have achieved microbiological success), the results of the random effects meta-analysis from the historical studies of nonantibacterial therapies can be used to define a treatment difference. Other infectious disease indications show that antibacterial drugs exert their greatest clinical effect on certain endpoints compared to placebo earlier during the course of therapy. Thus, it appears to be reasonable to provide an estimate of the treatment difference at an endpoint earlier in therapy for cUTI (i.e., at the time of IV-to-oral switch and therapy is ongoing).

An estimate of the treatment difference of an IV antibacterial drug can be derived from comparing the upper bound of the rate of microbiological success plus clinical response noted before antibacterial drug therapies were available (approximately 33 percent from Table 1), and the lower bound of the rate of microbiological success plus clinical response from recently conducted clinical trials of antibacterial drugs using the time point of a switch from IV to oral therapy (approximately 56 percent from Table 3). The treatment difference is estimated to be 23 percent (56 percent minus 33 percent).

The treatment difference is probably a conservative estimate of antibacterial effect, because symptoms do not disappear immediately, even if infection is suppressed. Because all patients achieved microbiological success during antibacterial drug therapy to which the bacteria are susceptible, the true treatment difference may be much larger than 23 percent observed.

On clinical grounds, an M_2 of 10 percent can be supported for active-controlled clinical trials of cUTI using a responder endpoint of microbiological success plus clinical resolution at a fixed time point of approximately 5 days of IV investigational drug therapy at the time of IV-to-oral switch, in the patient population with microbiologically documented cUTI. Trials evaluating the responder endpoint at the fixed time point of approximately 5 days of IV therapy should continue to follow patients throughout the course of therapy and a period of observation after completion of all therapy (e.g., approximately 7 days after completion of IV and oral drug therapy) for overall evaluation of safety and efficacy of the investigational IV drug.

Sample Size Calculations

The sample size of a clinical trial should be sufficient to provide the capability of providing statistically and clinically meaningful results of noninferiority of the investigational drug to an active-controlled drug for treatment of cUTI. The following is an example of the sample size calculations for a clinical trial enrolling patients with cUTI. Sponsors can follow this example when planning for phase 3 trials of cUTI.

We assumed the rate of clinical responders (microbiological success plus clinical resolution of symptoms) would be 75 percent in the active-controlled group. This is a reasonable estimate based on our retrospective review of data contained in recent new drug applications (see Table 2). We assumed a two-sided type 1 error (α) of 0.05 and type 2 error (β) of 0.20 (power 0.80), and a noninferiority margin of 10 percent. The sample size of the micro-ITT population is 295 patients per group. Assuming that 80 percent of the enrolled patients will have a bacterial pathogen isolated on urine culture, a total of 370 patients per group should be enrolled. Thus, a trial of about 750 patients, with 1:1 randomization to investigational drug or active-controlled drug, should provide adequate power for a determination of noninferiority on the responder endpoint of microbiological success plus resolution of clinical symptoms.

When the same assumptions are used except that β is 0.10 (power 0.90), the estimate of the total sample size is approximately 495 patients per group. We did not increase the sample size estimate to account for loss to follow-up or missing data. Loss to follow-up or counting missing data as failures can bias toward a finding of noninferiority. Because patients in a cUTI trial are evaluated and followed for a relatively short period of time and the clinical and microbiologic endpoints are readily and easily captured in patients, we anticipate that a trial should have few, if any, patients lost to follow-up.

These assumptions are conservative for the sample size estimate. For example, if the responder rate in the control group was 80 percent instead of 75 percent, and if a greater proportion of patients have a bacterial pathogen isolated on baseline urine culture (90 percent of patients enrolled instead of 80 percent), using the same assumptions about error (two-sided α of 0.05 and β of 0.20) and noninferiority margin of 10 percent, an estimate of approximately 280 patients per group can be used for a total sample size of approximately 560 patients. If the assumption is changed to a β of 0.10 (power 0.90), the estimate increases to approximately 375 patients per group, for a total sample size of approximately 750 patients. Previous phase 3 trials for this indication were conducted with sample sizes of approximately 500 patients to 750 patients per trial. It would be possible to adjust sample sizes according to interim estimates of blinded rates of the proportion with positive baseline urine cultures and pooled responder rates.